Journal of the American College of Cardiology Vol. 47, No. 7, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.11.052

Effects of Normal Aging on Left Ventricular Lusitropic, Inotropic, and Chronotropic Responses to Dobutamine

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OBJECTIVES The purpose of this study was to characterize how aging impacts the left ventricular (LV) functional reserve.

BACKGROUND Early diastolic LV filling slows markedly with advancing age, but the effects of β-adrenergic stimulation on filling, and its major determinant, relaxation, have not been investigated in an aging population. Although the responses of contractility and heart rate to catecholamines reportedly diminish with age, the effect of age on the responses to steady-state dobutamine infusions is unclear.

METHODS Groups of younger (40 ± 10 years, n = 26) and older (68 ± 11 years, n = 24) normal adult patients were studied at baseline and at three progressive dobutamine infusion dosages (5, 10, and 20 μg/kg/min). The LV function was evaluated by two-dimensional and Doppler echocardiography. Myocardial relaxation was evaluated from cardiovascular magnetic resonance (CMR)-based ρ, a preload-independent surrogate for τ. Effective LV pump-function index (PFi), defined as systolic blood pressure/end-systolic LV diameter, was measured.

RESULTS Both groups showed expected dose-dependent increases in heart rate and LV systolic function, diastolic function, and relaxation. Early LV filling reserve was much greater in younger than older patients (E-wave increase from baseline to highest dose, 24.0 vs. 9.5 cm/s, $p < 0.004$), although the dose responses of ρ were indistinguishable (0.18% vs. 0.19%/ms, $p = 0.22$). Whereas dobutamine caused a significantly greater increase of PFi in younger than older patients (30.1 vs. 15.6 mm Hg/cm, $p < 0.0001$), there was no difference in heart rate augmentation (37 vs. 38 beats/min, $p = 0.94$).

CONCLUSIONS Aging is accompanied by a blunted inotropic but preserved chronotropic response to steady-state dobutamine infusion. Although LV filling reserve declines with age, relaxation reserve does not. (J Am Coll Cardiol 2006;47:1440–7) © 2006 by the American College of Cardiology Foundation

An age-associated decline in resting early left ventricular (LV) diastolic function in normal adults is well documented using Doppler echocardiographic methods such as E- and A-wave velocities, E-wave deceleration, and isovolumic relaxation time. Despite the decline in diastolic function with age, studies that have examined inotropic measures such as fractional shortening or velocity of circumferential shortening at rest have seen little or no decline with advancing age (1,2). As important as resting measures of LV performance is the ability of the heart to show reserve capacity in response to stress. β-adrenergic stimulation by catecholamine administration is commonly used as a pharmacologic stress to determine the presence of significant coronary artery disease, and can be used to assess lusitropic, inotropic, and chronotropic reserves.

The impact of normal aging on LV lusitropic functional response to β-adrenergic agonists is unknown. Diastolic function is determined by a complex blend of myocardial relaxation, load, and stiffness; recently developed noninvasive methods for characterizing the response of each of these to adrenergic stimulation have not been applied toward the study of the aging heart. Numerous studies have shown a reduced inotropic functional response to isoproterenol, a potent stimulant of both β_1 and β_2 adrenergic receptors, with advanced age (3–7). In these studies, chronotropic responsiveness has also decreased with normal aging. However, it is unclear whether this difference in heart rate effect is mediated by age-associated decline in the baroreceptor response to β_2-mediated vasodilation rather than by intrinsic decreases in β_1-adrenergic responsiveness.

The current study was designed to characterize how age impacts the cardiac lusitropic, inotropic, and chronotropic responses to β-adrenergic stimulation in carefully screened normal adults. Diastolic and systolic LV performance was evaluated by echocardiographic techniques and recently

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Manuscript received February 8, 2005; revised manuscript received November 1, 2005, accepted November 7, 2005.

Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance
LV = left ventricular
PFi = pump function index
SBP = systolic blood pressure
ρ = slope of diastolic LV myocardial recoil; CMR-based recoil rate
τ = time constant of diastolic LV pressure decrease; measure of relaxation

developed and validated cardiovascular magnetic resonance (CMR) methods (8). The potential for a confounding baroreceptor effect on chronotropic response was minimized by using steady-state dobutamine infusions, which provide relatively selective agonism of β_1 rather than β_2 adrenergic receptors.

METHODS

Patients. Normal volunteers from the Baltimore Longitudinal Study of Aging (BLSA) were recruited for this study. This cross-sectional sample of 50 individuals ranged in age from 23 to 90 years, with a median age of 53 years. They were healthy, ambulatory, and community-dwelling, with no evidence of acute or chronic cardiovascular disease, no debilitating illnesses, and no cardiovascular medications. In addition, all individuals were screened for the absence of heart disease by medical history, physical examination, resting and exercise electrocardiogram, and, if ≥40 years of age, thallium scintigraphy. Individuals had a seated blood pressure <160/95 mm Hg on current physical examination. The median age was used to divide the sample into a younger (40 ± 10 years) and older (68 ± 11 years) cohort for performing age comparisons.

Dobutamine protocol. Identical stress protocols were used for magnetic resonance imaging and echocardiographic examinations on successive days. To ensure equivalent status at both examinations, they were performed at the same time of day on patients kept fasting from midnight until the test was completed. In addition, it was ensured that there was no change in medications between the two examinations. Data were acquired at baseline, and during 6-min stages of dobutamine infusions of 5, 10, and 20 μg/kg/min. Blood pressure, electrocardiogram, and transcutaneous oxygen saturation were monitored throughout the dobutamine imaging studies. Administration of dobutamine at a steady rate was chosen because it avoids the confounding effects of the baroreflex and is concordant with the usual diagnostic and therapeutic regimens for catecholamine infusion. Also, steady-state conditions are preferable for conducting CMR data acquisitions, which are lengthy.

CMR cine imaging. Cardiac magnetic resonance tissue tagging has allowed precise characterization of LV systolic and diastolic performance. The CMR-based LV recoil rate (ρ) has been shown to be a noninvasive, preload-independent predictor of LV relaxation (9). The net difference in short-axis twist between base and apex experienced throughout the cardiac cycle is defined as torsion. The rapid reversal of torsion in diastole is defined as recoil, with ρ, defined as the slope of isovolumic early recoil. Prior studies in our laboratory have shown that ρ correlates closely with invasively determined τ. Advances in CMR methods, particularly increased imaging speed, allow the performance of staged pharmacologic stress studies (10–12).

Tagged cine images were acquired on a Siemens Vision 1.5-T clinical imaging system (Siemens Medical Systems, Erlangen, Germany). A segmented k-space (segmentation level = 3) fast-gradient echocardiographic pulse sequence with view sharing was used to obtain prospectively gated breath-hold gradient echocardiographic cines, with radial tags applied at end diastole. Intrinsic cycle time was 30 ms, which, with view-sharing, resulted in cine temporal resolution of 20 ms. Rectangular field of view was used to limit acquisition time, with a 2:1 acquisition ratio of readout to phase encode resolution, resulting in a 256 × 256 image matrix. At each dobutamine dose, five separate cines were acquired; basal, mid-ventricular and apical short axis planes, and two-chamber and four-chamber long-axis planes.

Contouring and deformation analysis were performed offline using software developed in-house (Cardiac Image Processing System). Recoil rate (ρ) is defined as the slope of the line fit to recoil points measured during isovolumic relaxation, expressed as percent maximum torsion per microsecond.

Echocardiography. A variety of LV structural and functional indices were evaluated from echocardiographic stress examinations, obtained using a 3.5-MHz imaging transducer on a Phillips Sonos 5500 system (Phillips Medical Systems, Best, the Netherlands). Doppler echocardiography was used to measure transmitral velocities and physiological intervals using standard techniques, tissue Doppler long-axis mitral annulus velocities at the lateral wall, and color M-mode estimates of the velocity of propagation of the LV filling wave; two-dimensional echocardiography was used to measure LV dimensions, and an LV pump function index (PFi), defined as systolic blood pressure (SBP)/LV end-systolic cavity diameter, was calculated. Echocardiographic measurements were performed offline using personal computer-based ImageVue DCR software (Eastman-Kodak, Rochester, New York).

Statistical analysis. Statistical analyses were performed using the personal computer-based application StatView (SAS Institute Inc., Cary, North Carolina). Student t test was used to compare group measures at baseline. To examine the effect of age on structure and function, as well as possible gender interactions, repeated-measures analysis of variance was performed to compare dobutamine dose responses in the younger versus older groups. As a further test to evaluate the age dependence of catecholamine response, the change from baseline measures induced by maximum dose was regressed on age using linear regression analysis. A two-tailed p value < 0.05 was defined as

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statistically significant. Data are expressed as mean ± standard deviation.

RESULTS

Baseline age group differences. Basic descriptive group characteristics are shown in Table 1. The age groups did not differ significantly in either body mass index or body surface area. At baseline, younger patients had lower SBP and pulse pressure than older patients (see Table 2 for p values), but the groups had nearly identical heart rates.

Baseline echocardiographic and CMR indices of cardiac structure and function are compared in Table 2. Linear measures of LV dimension are indexed to body height; younger patients had generally thinner LV walls at end-diastole, including lower septal wall (0.56 ± 0.06 cm/m vs. 0.62 ± 0.07 cm/m, $p < 0.004$) and posterior wall (0.55 ± 0.07 cm/m vs. 0.61 ± 0.07 cm/m, $p < 0.005$) thicknesses; and larger LV cavity diameter (2.73 ± 0.27 cm vs. 2.53 ± 0.25 cm, $p < 0.013$). Several baseline measures indicated better early diastolic function and lesser late diastolic function in younger than in older patients, including greater peak E-wave velocity (84 ± 22 cm/s vs. 73 ± 17 cm/s, $p < 0.03$); shorter deceleration time of early transmitral flow (187 ± 33 ms vs. 225 ± 61 ms, $p < 0.01$); lower peak A-wave velocity (64 ± 11 cm/s vs. 79 ± 17 cm/s, $p \leq 0.0004$); and lower overall A-wave velocity-time integral (5.7 ± 1.2 cm vs. 7.4 ± 2.3 cm, $p \leq 0.001$). Isovolumic relaxation time was shorter in younger (79 ± 15 ms vs. 85 ± 15 ms, $p \leq 0.04$), whereas myocardial ρ at baseline was not significantly different between the younger and older groups, respectively (0.61 ± 0.20%/ms vs. 0.55 ± 0.16%/ms, $p = 0.17$).

Resting heart rate was similar in younger and older patients, (69 ± 10 beats/min vs. 68 ± 7 beats/min); however, PFi was lower in younger patients (39 ± 7 mm Hg/cm vs. 47 ± 12 mm Hg/cm, $p \leq 0.008$); and younger patients had a shorter ejection time (285 ± 17 ms vs. 308 ± 23 ms, $p \leq 0.0003$). In contrast, thickening of the septum (29 ± 6% vs. 23 ± 6%, $p < 0.01$) and posterior free wall (30 ± 6% vs. 24 ± 7%, $p < 0.02$) were higher in younger than in older patients. No significant difference in endocardial fractional shortening was seen between age groups at baseline.

Table 1. Subject Characteristics

	Younger Group, Age < Median (n = 26)	Older Group, Age ≥ Median (n = 24)
Age (yrs)	40 ± 10	68 ± 11
% women	42	58
BMI	26.0 ± 4.6	25.5 ± 3.4
BSA (m^2)	1.90 ± .25	1.80 ± 25
SBP (mm Hg)	123 ± 17	128 ± 14
DBP (mm Hg)	73 ± 10	71 ± 9
PP (mm Hg)	49 ± 16	57 ± 12
HR (beats/min)	69 ± 10	68 ± 7

BMI = body mass index; BSA = body surface area; DBP = diastolic blood pressure; HR = heart rate; PP = pulse pressure; SBP = systolic blood pressure.

Table 2. Comparisons of Baseline Values Between Age Groups

	Younger Group, Age < Median	Older Group, Age ≥ Median	p t Test
	Baseline	Baseline	Baseline
Chronotropy			
Heart rate (beats/min)	69 ± 10	68 ± 7	0.7615
Blood pressure			
Systolic blood pressure (mm Hg)	123 ± 17	128 ± 14	0.2440
Diastolic blood pressure (mm Hg)	73 ± 10	71 ± 9	0.4076
Pulse pressure (mm Hg)	49 ± 16	57 ± 12	0.0688
LV structure			
Diastolic septal thickness index* (cm/m)	0.56 ± .06	0.62 ± .07	**0.0031**
Diastolic post wall thickness index* (cm/m)	0.55 ± .07	0.61 ± .07	**0.0045**
Diastolic cavity diameter index* (cm/m)	2.73 ± .27	2.53 ± .25	**0.0128**
Left atrial linear dimension index* (cm/m)	1.95 ± .29	2.17 ± .37	**0.0320**
LV pump function			
Pump function index (mm Hg/cm)	39.4 ± 7.2	46.5 ± 11.5	**0.0080**
End systolic cavity diameter index* (cm/m)	1.91 ± .32	1.70 ± .25	**0.0106**
Septal thickening (%)	29 ± 6	23 ± 6	**0.0092**
Posterior wall thickening (%)	30 ± 6	24 ± 7	**0.0172**
Annular velocity in systole (cm/s)	12.2 ± 4.3	12.5 ± 8.6	0.9175
Endocardial fractional shortening (%)	30 ± 6	33 ± 9	0.1401
Velocity of circumferential shortening (%/ms)	0.10 ± .02	0.10 ± .03	0.6360
LV relaxation			
Recoil rate (%/ms)	0.61 ± .20	0.55 ± .16	0.1681
Velocity propagation (cm/s)	56.8 ± 16.5	50.9 ± 23.6	0.3958
Annular velocity in early diastole (cm/s)	18.1 ± 7.0	13.0 ± 9.2	0.0941
Annular velocity in late diastole (cm/s)	13.2 ± 5.9	14.2 ± 4.9	0.6525
LV filling			
Peak E-wave filling velocity (cm/s)	84.3 ± 21.9	72.8 ± 17.3	**0.0258**
Peak A-wave filling velocity (cm/s)	63.6 ± 10.9	79.2 ± 16.9	**0.0004**
Deceleration time (ms)	187 ± 33	225 ± 61	**0.0099**
Deceleration rate (cm/s^2)	477 ± 164	351 ± 112	**0.0012**
E-wave velocity-time integral (cm)	12.1 ± 3.1	11.1 ± 3.5	0.2855
A-wave velocity-time integral (cm)	5.7 ± 1.2	7.4 ± 2.3	**0.0010**
Isovolumic relaxation time (ms)	78.5 ± 15.3	84.6 ± 14.9	**0.0400**

*Measures indexed to height in meters. **Bold** values indicate statistical significance at a level of $p < 0.05$.
LV = left ventricular.

Table 3. Comparisons of Responses to Graded Dobutamine Infusion, Y Versus O

	Dose Response (Mean Change From Baseline)						ANOVA (Repeated Measures)			Regression (Change at Maximum Dose)		
	75 μg/kg/min		10 μg/kg/min		20 μg/kg/min		p	p	p	m	r	p
	Y	O	Y	O	Y	O	Age	Dose	Inter	Age	Age	Age
Chronotropy												
Heart rate (beats/min)	1	−1	9	9	37	38	0.6877	**<0.0001**	0.9422	0.102	0.103	0.5225
Blood pressure												
Systolic blood pressure (mm Hg)	4	5	23	15	40	24	0.9870	**<0.0001**	**0.0079**	−0.339	−0.312	**0.0473**
Diastolic blood pressure (mm Hg)	0	2	3	−1	4	−2	0.1017	0.7118	**0.0101**	−0.188	−0.331	**0.0370**
Pulse pressure (mm Hg)	4	4	19	17	36	27	0.3558	**<0.0001**	0.3177	−0.146	−0.155	0.3394
LV structure												
Diastolic septal thickness index* (cm/m)	−0.01	0.01	0.02	0.02	0.02	0.06	**0.0002**	**0.0007**	0.1274	0.002	0.342	**0.0216**
Diastolic post wall thickness index* (cm/m)	−0.01	0.02	0.01	0.03	0.03	0.06	**0.0002**	**0.0006**	0.5619	0.001	0.196	0.2016
Diastolic cavity diameter index* (cm/m)	0.03	0.00	−0.06	0.00	−0.10	−0.09	**0.0196**	**0.0032**	0.5671	0.000	0.021	0.8911
Left atrial linear dimension index* (cm/m)	0.05	−0.08	−0.00	−0.11	−0.05	−0.17	0.2185	**0.0002**	0.0567	−0.003	−0.218	0.1664
LV pump function												
Pump function index (mm Hg/cm)	4.4	4.1	20.3	8.0	30.1	15.6	0.7697	**<0.0001**	**0.0002**	−0.345	−0.436	**0.0100**
End systolic cavity diameter index* (cm/m)	−0.09	−0.07	−0.34	−0.10	−0.41	−0.24	0.2983	**<0.0001**	**0.0064**	0.009	0.386	**0.0105**
Septal thickening (%)	−0	2	1	1	3	−1	**0.0003**	0.8670	0.1638	−0.086	−0.196	0.2074
Posterior wall thickening (%)	1	2	3	1	2	0	**0.0002**	0.4192	0.5386	0.013	0.028	0.8587
Annular velocity in systole (cm/s)	2.4	0.3	6.3	5.1	7.3	8.6	0.9339	**0.0012**	0.8690	0.104	0.139	0.4908
Endocardial fractional shortening (%)	5	3	13	4	14	7	0.5971	**<0.0001**	**0.0060**	−0.002	−0.332	**0.0295**
Velocity of circumferential shortening (%/ms)	0.03	0.02	0.08	0.05	0.12	0.09	0.1872	**<0.0001**	0.1121	−0.001	−0.273	0.0888
LV relaxation												
Recoil rate (%/ms)	−0.07	0.05	0.10	0.07	0.18	0.19	0.3359	**<0.0001**	0.2203	0.002	0.151	0.3857
Velocity propagation (cm/s)	15.9	18.8	22.4	22.8	21.1	20.6	0.4658	**<0.0001**	0.9865	−0.049	−0.033	0.8607
Annular velocity in early diastole (cm/s)	0.2	−0.5	1.6	1.4	0.9	1.0	0.0138	0.4897	0.9919	−0.005	−0.011	0.9562
Annular velocity in late diastole (cm/s)	−0.2	2.2	1.4	4.0	1.5	4.0	0.1726	**0.0078**	0.4423	0.048	0.167	0.3945
LV filling												
Peak E-wave filling velocity (cm/s)	11.2	5.6	21.7	8.3	24.0	9.5	**0.0011**	**<0.0001**	**0.0033**	−0.486	−0.483	**0.0006**
Peak A-wave filling velocity (cm/s)	4.8	2.0	12.0	12.4	20.9	22.2	**0.0010**	**<0.0001**	0.7308	0.044	0.059	0.6907
Deceleration time (ms)	16	25	12	24	11	−6	**0.0004**	**0.0300**	0.3545	−0.510	−0.142	0.3357
Deceleration rate (cm/s^2)	4	−16	87	−4	73	59	**<0.0001**	**0.0048**	0.2046	0.064	0.006	0.9677
E-wave velocity-time integral (cm)	1.8	2.1	3.6	2.1	3.2	−0.2	**0.0345**	**<0.0001**	**0.0023**	−0.117	−0.481	**0.0006**
A-wave velocity-time integral (cm)	0.4	0.4	0.6	1.2	1.1	1.6	**0.0003**	**<0.0001**	0.5090	0.009	0.093	0.6907
Isovolumic relaxation time (ms)	−3.8	−9.3	−13.7	−16.8	−18.5	−27.4	0.6736	**<0.0001**	0.1684	−0.311	−0.390	**0.0097**

*Measures indexed to height in meters. **Bold** values indicate statistical significance at a level of $p < 0.05$.
LV = left ventricular; m = slope of fit line; O = older group, age > median; r = correlation coefficient of linear regression; Y = younger group, age < median.

Dose responses of young versus older groups to dobutamine. Dobutamine dose response differences between younger and older patients are shown in Table 3. In addition to the observed deficit in early diastolic function of older patients at baseline, they also showed a markedly muted augmentation of peak E-wave velocity (+24.0 vs. +9.5 cm/s, younger vs. older patients, $p < 0.004$) (Fig. 1) and velocity-time integral (+3.2 vs. −0.2, $p < 0.003$) in response to dobutamine; both of these measures also showed enhancements that were significantly correlated with age. No age difference in peak A-wave velocity augmentation was observed (Fig. 2). Whereas the shortening of isovolumic

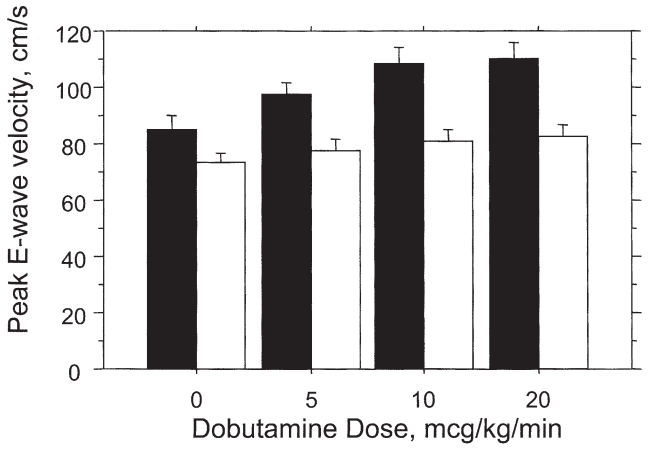

Figure 1. Early diastolic left ventricular filling, as indicated by Doppler echocardiographic peak E-wave velocity (E-peak), is lower in the older **(open bars)** than younger **(solid bars)** group at baseline. Moreover, E-peak increases with dobutamine dose in the younger but not the older group (interaction $p < 0.004$). Error bars = 1 SEM.

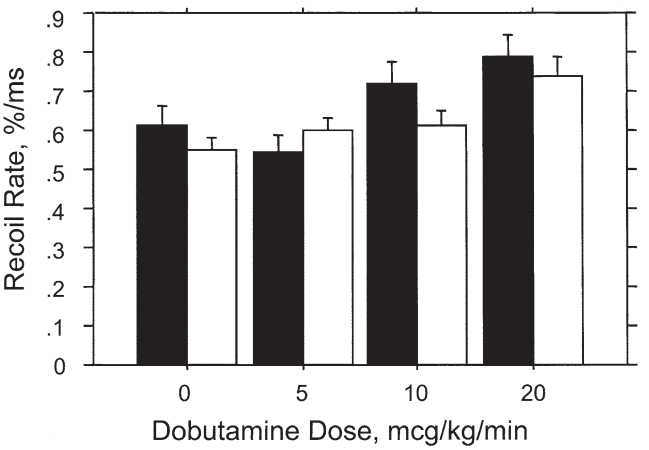

Figure 3. Left ventricular relaxation, as indicated by magnetic resonance imaging recoil rate (r) expressed as percent of maximum torsion per microsecond, increases generally with dobutamine dose; this dose response is indistinguishable between the two age groups. **Solid bars** = younger; **open bars** = older. Error bars = 1 SEM.

relaxation time in response to dobutamine was not significantly different between age groups, the shortening of isovolumic relaxation time induced by maximal dose decreased significantly with age ($r = -0.39$, $p < 0.01$). No measure of LV relaxation, including ρ (Fig. 3), LV flow velocity propagation, and early diastolic tissue Doppler mitral valve annulus velocity, showed a different augmentation pattern between younger and older patients.

A generally reduced pump function dose response to catecholamine infusion was seen in older patients (Fig. 4), including LV end systolic cavity dimension (−0.41 vs. −0.24 cm/m, younger vs. older patients, $p < 0.007$) and endocardial fractional shortening (+14% vs. +7%, $p \leq 0.006$), and again, these results were reinforced by a significant correlation between induced changes in pump function and age (Table 3). The augmentation in SBP was significantly greater in younger than older patients (+40 vs. +24 mm Hg, $p < 0.008$). Thus, the PFi was inversely correlated with age. Percent wall thickening, however, increased similarly with dose in both groups. Despite the generally greater LV pump function response showed by younger patients, no such age difference was seen in chronotropic responsiveness to catecholamine infusion; heart rate increased in younger patients from 69 to 106 beats/min and in older patients from 68 to 106 beats/min (Fig. 5).

Because there was a modest, non-significant difference in gender composition of the two age groups, (42% vs. 58% female in younger vs. older groups), we tested for interactions between age and gender that might affect the significance of observed differences in dobutamine responses. No interaction was found except in the response of SBP ($p < 0.05$ for gender-age interaction response), where the higher percentage of women in the older group, along with a lower dose response among women (+27 vs. +38 mm Hg for men, $p < 0.008$), contributed to the observed reduction in

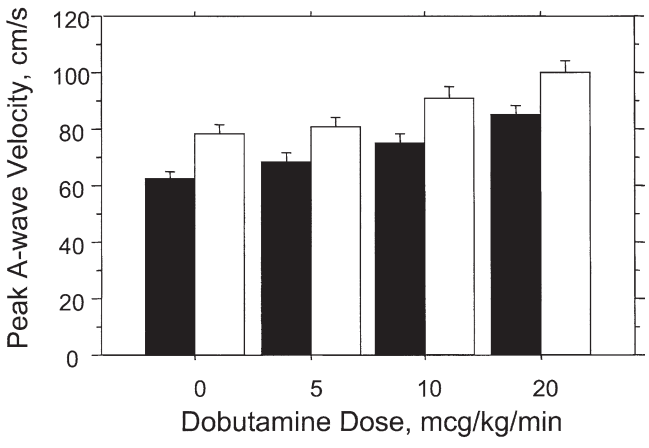

Figure 2. Late diastolic left ventricular filling, as indicated by Doppler echocardiographic peak A-wave velocity (A-peak), increases with dobutamine dose in both groups. Whereas younger **(solid bars)** patients have lower overall A-peak than older **(open bars)** patients, the dose response to dobutamine is indistinguishable between the two age groups. Error bars = 1 SEM.

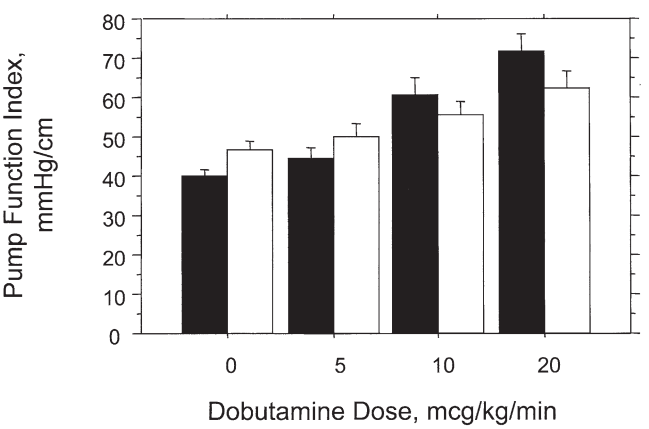

Figure 4. Although pump function index (PFi) defined as systolic blood pressure (SBP)/left ventricular (LV) end-systolic cavity dimension, is lower in the younger group **(solid bars)** at baseline, its response to increasing doses of dobutamine is greater than in the older group **(open bars)** (interaction $p < 0.0001$). Error bars = 1 SEM.

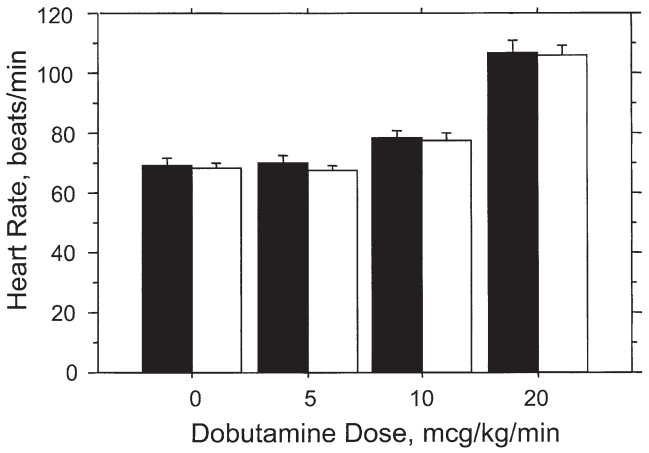

Figure 5. Heart rate is similar at rest and increases with dobutamine dose, with nearly identical dose responses in the two age groups. **Solid bars** = younger; **open bars** = older. Error bars = 1 SEM.

dose response with age. The much greater enhancement in PFi of younger than older patients did not share this gender interaction.

DISCUSSION

These data show that the LV response to steady-state dobutamine infusion differs in normal young and older adults in several ways. Diastolic function, particularly early LV filling, augments to a greater extent in response to increasing dobutamine dose in young individuals, although this cannot be attributed to greater augmentation of LV relaxation. Several measures suggest a greater inotropic response to β-adrenergic stimulation in younger individuals, although the chronotropic response of older and younger patients is virtually indistinguishable in these healthy volunteers.

Relation of age to lusitropic effects of dobutamine. Early diastolic filling is dependent on myocardial relaxation. The reduced early diastolic filling rates seen in elderly patients are usually ascribed to age-related changes in the rate of LV pressure decrease. However, recent studies do not support this concept. Using invasive methods, Yamakado et al. (13) reported measures of relaxation by micromanometer in 55 normal patients ages 20 to 77 years, and τ was not related to age. These findings are consistent with our recent study using echocardiography (filling wave velocity propagation and tissue Doppler echocardiography) and CMR (ρ) measures in a similarly normal sample of 122 patients, also derived from the BLSA trial (8). Specifically we found no age-associated change in relaxation, despite the decline in early LV filling with age.

To further understand the effects of age on diastolic function, the current study examined filling and relaxation reserve in response to catecholamine stress. Here, the observed group differences in early peak filling rate augmentation were evidently not mediated through changes in relaxation, measured by several methods, including ρ, LV flow velocity propagation, and early diastolic tissue Doppler mitral valve annulus velocity. In each of these measures of relaxation, indistinguishable augmentation patterns to dobutamine were seen in young and older individuals, despite a markedly reduced enhancement pattern of early filling seen in older patients.

Left ventricular filling is mediated by transmitral hemodynamics. If ventricular relaxation does not drive the atrial-ventricular pressure gradient, preload emerges as the most reasonable explanation. Lenihan et al. (14) studied the effect of altering load (with nitroprusside and phenylephrine) and contractility (with dobutamine) on the early diastolic atrioventricular gradient and on LV filling in patients with diastolic dysfunction caused by hypertension. They found that changes in the atrioventricular gradient were determined primarily by loading conditions and were not importantly influenced by LV relaxation. For example, dobutamine reduced early filling velocities in their study despite a distinct augmentation in relaxation, because small declines in LA pressure caused by venodilation had a much greater impact on filling than did the rate of LV pressure decrease. A similar interaction between relaxation, preload, and filling was probably operative in our older cohort. However, these individuals experienced only reduced filling augmentation rather than an actual filling decline, perhaps because they manifested only normal age-related diastolic dysfunction rather than the more marked dysfunction induced by disease.

Relation of age to inotropic and chronotropic effects of dobutamine. The response to β-adrenergic stimulation by isoproterenol, including sharply increased heart rate and contractility, has generally been found to be attenuated in older individuals (3–7). Our findings differed in part from this pattern; as anticipated, the older group did show a lesser response in PFi to dobutamine, whereas the chronotropic effects were virtually identical between groups. Because the chronotropic response is influenced by both sympathetic and parasympathetic nervous systems, the difference in findings in various studies may be attributable to a different contribution of parasympathetic baroreceptor reflexes in each. Stratton et al. (15) reported that vagally mediated parasympathetic effects on heart rate decreases with age. This might be caused by age-related arterial stiffening, muting the baroreceptor reflex. Therefore, prior reports of diminished chronotropic response to β-agonists with aging may reflect in part diminished parasympathetic withdrawal in response to β_2-mediated vasodilatation rather than solely diminished sympathetic response. In support of this concept, in pithed rats, in which the baroreflex was eliminated, the age-related deficit in heart rate response to a catecholamine bolus seen in intact animals was eliminated (16). In our study we used dobutamine, which has only weak β_2 activity, and is thus less likely to cause baroreflex-mediated tachycardia. In addition, the drug was administered as a sustained infusion, allowing time for the baroreceptor response to extinguish before responses were measured. Thus, measurements immediately after bolus administration of

catecholamines might reflect a transient baroreceptor-mediated deficit in heart rate response in the elderly, which could then ameliorate when the longer-term infusion allows the full, steady-state response to occur. In support of this concept, Poldermans et al. (17) also found no age-associated deficit in chronotropic response to staged, steady-state infusions of dobutamine in patients referred for diagnostic pharmacologic stress testing, paralleling our own findings. Notably, isoproterenol was used in all (3–7) studies that showed a reduced chronotropic response to β-agonists in aged individuals.

There are several possible explanations for the dissociated inotropic and chronotropic β_1 adrenergic responses with age. First, these results raise the possibility that distinct β_1 receptor subtypes modulate inotropic versus chronotropic responses, and aging may have a selective effect on certain subtypes. Using the noncardioselective β-receptor blocker mepindolol with increasing isoproterenol dose in a small cohort of normal men, Bonelli (18) effected selective blockade of positive inotropic and positive chronotropic responses. These dissociated inotropic and chronotropic dose responses were interpreted as evidence that distinct β_1 receptors mediate specific effects on heart rate and positive inotropy.

Second, there may be an age-related difference in the distribution of β-receptors in the right atrium versus the left ventricle, explaining differential chronotropic and inotropic responses to β-adrenergic stimulation. This seems to be the case in chronic hypoxia, in which a similar maintained chronotropic but reduced inotropic response to catecholamines was seen by Doshi et al. (19).

Study limitations. The dobutamine regimen chosen for this study is somewhat conservative when compared with common clinical protocols. However, inotropic parameters such as percent thickening, percent shortening, fractional shortening, and ejection fraction tend to plateau at or near these lower dobutamine doses. This effect is likely caused by the reduced preload, from venodilation, which occurs with dobutamine infusion at higher doses. Our decision to limit the drug dose was influenced by this plateau effect and also by our desire to limit potential adverse effects, such as arrhythmias, that might occur in normal volunteers during the time that they were undergoing CMR, particularly because rigorous electrocardiographic monitoring is not possible in the magnetic environment.

Another limitation of the current study is that brachial artery measurements of SBP do not necessarily reflect pressure in the LV, especially given possible age differences in the effect of dobutamine on pulse wave amplification. Therefore, it is more accurate to consider the ratio of SBP/LV systolic diameter as a relevant index of effective LV pump function rather than a true measure of LV contractility, for which it is an imperfect surrogate. The fact that other measures of LV pump function that do not incorporate peripheral blood pressure, most notably LV systolic diameter and fractional shortening, also showed reduced responses to dobutamine in the older group, does, however, support the concept of an age-associated deficit in contractility.

CONCLUSIONS

Cardiovascular responsiveness to graded dobutamine stress varies with normal aging. The CMR-based LV recoil rate (ρ), a novel, noninvasive surrogate for τ, does not indicate a significant loss of relaxation reserve in response to dobutamine with normal aging, which is similar to results obtained using direct micromanometer catheter measures (14). However, early LV filling reserve is significantly diminished with age, despite preserved myocardial relaxation reserve. These findings suggest, therefore, that age-related filling differences may reflect an altered left atrium-LV pressure gradient, through age-related changes in load or timing rather than simply altered relaxation. Normal aging is also accompanied by a blunted inotropic but not chronotropic response to steady-state exogenous β-adrenergic stimulation.

The steady-state response to graded dobutamine infusion provides insight into β-adrenergic responsiveness without the confounding influence of the baroreflex; this is in contrast to bolus doses, in which the baroreflex dominates. The clinical relevance of this distinction lies in the opportunity to determine whether the steady-state dobutamine doses used for diagnostic and therapeutic purposes should be altered in older individuals. The current findings, coupled with those of Poldermans et al. (14), suggest no need for such a dobutamine dose adjustment to increase heart rate. However, older patients may require larger doses than younger patients to achieve similar increases in pump performance.

Acknowledgments

The authors thank Ms. Stephanie Bosley and Ms. Joy Henderson for their work in performing these studies, as well as Ms. Susan Livengood for her help in data analysis. The authors are also grateful to the Baltimore Longitudinal Study of Aging (BLSA) participants who volunteered for this study.

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